Using Nanoparticle Shape as a Parameter in Drug Delivery

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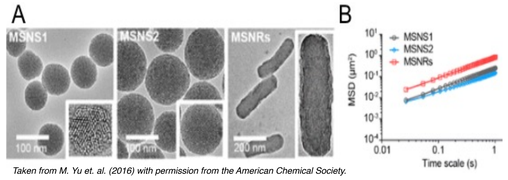
Introduction

Nanomedicine has been increasingly used recently over traditional approaches due to its increased bioavailability and biodistribution, enhanced penetration through the endothelial wall, low immunogenic effect, and easy customizability. However, it runs into a major obstacle: biological gels. Extracellular matrices (ECM) that surround cells inhibit efficient drug delivery, as their mesh-like structure captures these nanoparticles (NP)clear them through phagocytosis. With this, there is a need to further develop drug delivery systems to increase their efficacy and retention within the body.



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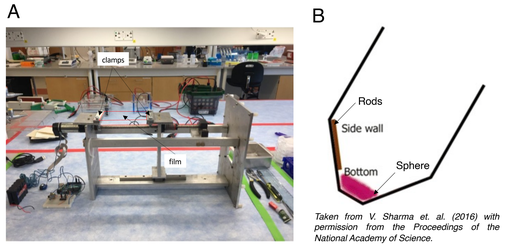
Nanoparticle shape has been a factor to enhance its diffusion through ECM. (A) 100nm, 200nm, and 200nm rod mesoporous silica nanospheres were tracked in gastrointestinal mucus *in vitro*. (B) Mean square displacements (MSDs) of the three types of nanoparticles in gastrointestinal mucus in a time scale of 1 second show that the rods diffused faster than the other spherical NPs.

In this work, we aim to show that shape plays an important role in affecting nanoparticle drug diffusion.

Methods

Rod-shaped nanoparticles are synthesized from stretching 100nm, 200nm, and 500nm spherical shaped fluorescent polystyrene nanoparticles. The process involves embedding the spherical NPs into an elastic polyvinyl film, liquifying the NPs in toluene, stretching the film using a mechanical stretcher (**A**). Centrifugation will be used to separate the unstretched spherical nanoparticles from the stretched sample (**B**).



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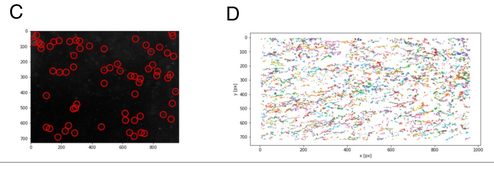
To analyze rod-shaped NP diffusion, fluorescence microscopy was used to capture videos. These videos were analyzed using TrackPy, a Python-based multiple particle tracking code that identifies objects in a frame (**C**), plots their trajectories (**D**), and calculates the mean square siplacement (MSD).



Using the MSDs at a lag time τ of 1 second, **Eq. 1** was used to calculate the diffusion coefficient, which is derived from the Stokes-Einstein Equation (**Eq. 2**). For rod-shaped NPs, a modified version of the equation was used (**Eq. 3**).

MSD related to *D*

(Eq. 1) $\langle MSD \rangle = 6Dt$

Stokes-Einstein Equation

(Eq. 2) $D = \frac{k_B T}{6\pi\eta R}$

Stokes-Einstein Equation derived for rod diffusion

(Eq. 3) $D^t(p) = (\frac{k_B T}{6\pi\eta L})(D_{||} + 2D_{\perp})$

where,

$D_{||}(p) = \ln(p) + \frac{-0.4536p^2 - 1.772p + 41.5}{p^2 + 34.38p + 18.96}$

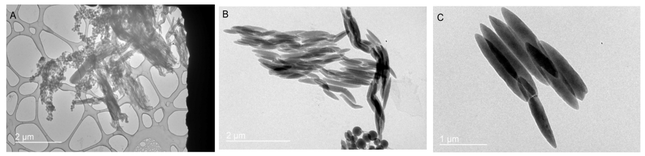
and

$D_{\perp}(p) = \ln(p) + \frac{-0.3604p^2 - 28.36p + 72.63}{p^2 + 36.29p + 34.9}$

Constants

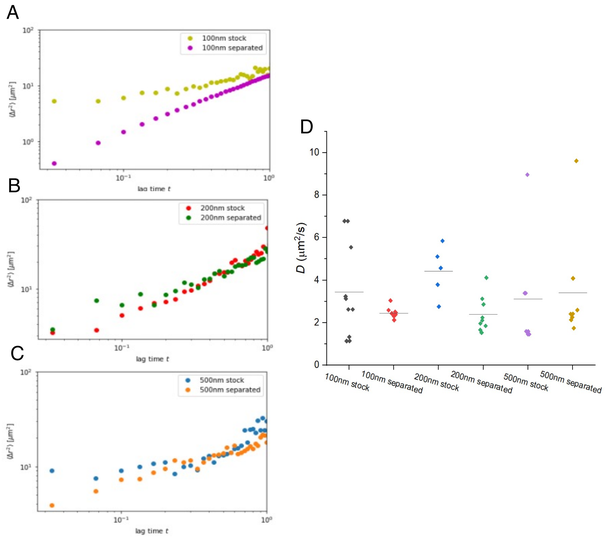
k_B: Boltzmann's constant
T: absolute temperature
t: lag time
R: spherical radius
η: dynamic viscosity
L: rod length
p: rod aspect ratio (L/w)

Nanoparticle Stretching Procedure Yields a Significant Amount of Rod-Shaped Nanoparticles



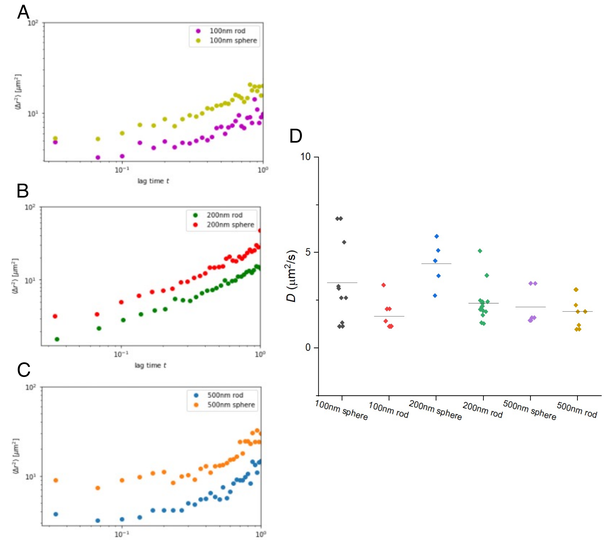
Images of stretched nanoparticle samples through transmission electron microscopy indicate that the sample is heterogenous with a combination of spheres and rods. ImageJ was used to characterize the dimensions of these rod-shaped NPs. (**A**) 100nm stretched nanoparticles (n = 109) have a length of 0.302 ± 0.0184nm and a width of 0.058 ± 0.007nm. (**B**) 200nm stretched nanoparticles (n = 105) have a length of 0.705 ± 0.132nm and a width of 0.126 ± 0.021nm. (**C**) 500nm stretched nanoparticles (n = 99) have a length of 1.77 ± 0.208 and a width of 0.285 ± 0.016.

Centrifugation Effectively Separates Rods and Spheres



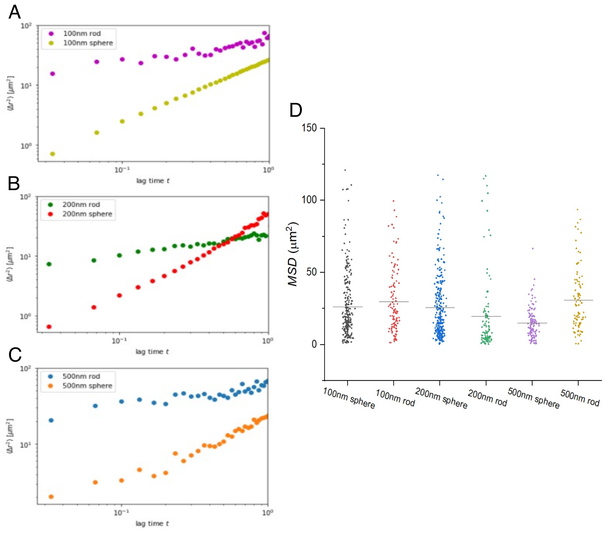
The diffusions between unstretched nanoparticles (stock) and the separated stretched spheres diffusion were compared by plotting their MSDs over lag time τ. (**A**) 100nm unstretched stock NPs diffused slightly faster, while both series for (**B**) 200nm and (**C**) 500nm NPs exhibited similar MSDs. (**D**) MSDs at τ = 1 s were used to calculate the average diffusion coefficients for each video, which are graphed using a scatter distribution plot.

Rod-Shaped Nanoparticles Exhibit Lower MSDs in Water



The diffusions between unstretched spherical nanoparticles and stretched rod-shaped nanoparticles in water were compared by plotting their MSDs over lag time τ. For (**A**) 100nm, (**B**), 200nm, and (**C**) 500nm NPs, the spheres diffused faster than the rods. (**D**) MSDs at τ = 1 s were used to calculate the average diffusion coefficients for each video, which are graphed using a scatter distribution plot.

Rod-Shaped Nanoparticles Exhibit Higher MSDs in MaxGel



The diffusions between unstretched spherical nanoparticles and stretched rod-shaped nanoparticles in MaxGel were compared by plotting their MSDs over lag time τ. For (**A**) 100nm, (**B**), 200nm, and (**C**) 500nm NPs, rods generally diffused faster than the spheres. (**D**) MSDs at τ = 1 s were collected for every single NP and graphed on a scatter distribution plot

Conclusion

- The nanoparticle stretching procedure produced a **heterogenous sample of spheres and rods**.
- Separation using centrifugation **separated the spheres from the rods**.
- Rod-shaped nanoparticles **exhibited lower MSDs** in water, indicating there was **a large enough morphological change**.
- Rod-shaped nanoparticles **exhibited higher MSDs** in MaxGel, indicating **that the rods diffused faster that the spheres**.
- Using a rod shape can **potentially enhance nanoparticle drug diffusion clinically**.

Future Directions

The Effect of PEGylation on Rod-Shaped Nanoparticle Diffusion

The covalent attachment of polyethylene glycol (PEG) to the surface of a nanoparticle is a common method used to enhance the circulation and retention of drugs and therapeutic. We are interested to see to what degree can PEGylation increase the diffusion rate of rod-shaped nanoparticles.

Clinical Translation

We wish to observe the diffusion of rod-shaped nanoparticles in clinical pulmonary mucus sourced from cystic fibrosis patients from the cardio-thoracic intensive care unit (CT-ICU) at the University of Maryland Medical Center. This will show how rod-shaped NPs will diffuse in more viscous, diseased states of biological gels.

Polystyrene is not a suitable material to use clinically due to its cytotoxic effects when broken down. Thus, a more biodegradable material such as Poly(lactic-co-glycolic acid) (PLGA) should be used instead, and the stretching procedure should be adapted accordingly.

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